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The Open University's first one day symposium on treatment-emergent neuroendocrine prostate cancer

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Abstract

The Open University's first one day symposium on treatment-emergent neuroendocrine prostate cancer attracted world-leading figures, early career researchers, and industry colleagues. The symposium proved insightful into the 'real-world' impact and current problems faced in the diagnosis and treatment of neuroendocrine prostate cancer. It was important for this meeting to take place as the incidence of NEPC is increasing due to the widespread use of next-generation androgen deprivation drugs.

The symposium discussions proposed new molecularly-driven deadlines to accelerate research and improved the treatment of this deadly and poorly recognised malignancy.

Keywords: neuroendocrine prostate cancer; cancer biomarkers; epigenetics; long non-coding RNAs; osteopontin; tumour microenvironment

Introduction

Treatment-emergent neuroendocrine prostate cancer (NEPC) is a recently identified clinico-pathological subtype of prostatic neoplasm, which is characterised by dismal prognosis and complete resistance to any hormonal therapy [1]. The Open University's hosted its first one day symposium entitled 'Treatment-emergent neuroendocrine prostate cancer' on 25th June 2019. The symposium attracted 39 clinicians, researchers and students from across the UK and internationally, who gathered to share, hear and debate the very latest developments in neuroendocrine prostate cancer research.

The programme featured keynotes from world-leading figures, early career researchers, and industry colleagues, proving impactful insights and current problems faced in the diagnosis and treatment of NEPC. A broad range of topics were covered including clinical diagnosis, molecular mechanisms of disease progression, and the development of novel biomarkers and therapeutics.

Highlights

Highlights of the first session included an insight into the clinical progression of prostate cancer. Professor Hardev Pandha, director of the Surrey Cancer Centre (Surrey UK), described the clinical presentation of prostate cancer and his experience managing neuroendocrine disease. Prof Pandha highlighted difficulties associated with diagnosing this complex pathology, and also the problems associated with second-line anti-androgens (abiraterone, enzalutamide). The lecture concluded by recommending re-biopsy of patients with suspected NEPC in order to improve accurate diagnosis (i.e. not waiting for treatment failure) and in doing so also treating patients more specifically and also increasing research material for better understanding this disease.

Following Professor Pandha's presentation, Dr Francesco Crea, Senior Lecturer at The Open University (Milton Keynes UK), discussed the cellular origins of prostate cancer and the 'classical' model of NEPC development [2]. Classically NEPC was thought to arise from oncogenic transformation of basal cells, distinct from the oncogenic transformation of luminal cells which give rise to prostatic adenocarcinoma [3]. However this model has been challenged by several studies [4,5]. These studies provide evidence that prostatic adenocarcinomas treated with second-line anti-androgens may give rise to either CRPC, or NEPC through a largely mechanistically unknown trans-differentiation process. Both Prof. Pandha and Dr Crea stated that the incidence of NEPC is likely to

rise with increased use of second line anti-androgens, and recommended re-biopsying patients with suspected NEPC after therapy.

To conclude the morning's clinical session, a discussion including Dr Jake Micallef from biotechnology company Volition (Isnes Belgium), Prof. Pandha, Dr Crea, and Mr Henry Andrews, a urologist from Milton Keynes Hospital then took place. The panel briefly introduced themselves and the audience then insightfully and openly discussed with the panel how the NEPC community can work together to change current guidelines. This change in guidelines is necessary to improve not only rapid diagnosis, but unnecessary use of ineffective treatments. It is only then we can begin to identify effective treatments against this disease. To underscore the importance of new guidelines, Dr Pandha presented 2 clinical cases in both cases biopsies were taken from CRPC patients that had shown progression after abiraterone or enzalutamide treatment. In both cases, the hormonal therapy was substituted by platinum-based chemotherapy. Dr Pandha stated that since June 2018 his Cancer Centre had identified and treated 7 NEPC patients, identified by soft tissue biopsies. For the Surrey NEPC project Prof. Pandha indicated that they would radiologically monitor 100 CRPC patients and biopsy when clinically indicated, as well as work to develop serum markers in order to improve diagnosis.

In the afternoon session, the molecular mechanisms of NEPC initiation and progression were discussed. Prof Yuzhuo Wang from the BC Cancer Agency (Vancouver Canada) gave a lecture on his lab's approach to the challenge of targeting NEPC using a pipeline ranging from discovery to drug development. Prof. Wang first described the expression and function of HP1a knock-down in various NEPC models demonstrating that this protein regulates NEPC cell survival and growth [6]. Prof Wang further described that HP1a also induces the neuroendocrine phenotype in prostatic adenocarcinoma cells upon over-expression. Mechanistically Prof Wang then described that HP1a works by enriching histone 3 lysine trimethylation (H3Kme3) on AR and REST promoters which represses their expression, promoting the NEPC phenotype. Concluding this data Prof Wang suggested HP1a as a serum marker, and as a druggable target to prevent trans-differentiation to NEPC, and for NEPC. Prof. Wang then described another target identified by his lab after going back to one of the fundamental hallmarks of cancer, evasion of the immune response. MCT4, a transporter protein, was identified in prostate cancer as a possible immune regulator [7]. This protein is a transporter involved in glycolytic phenotypes. By designing anti-sense oligonucleotides against this protein, the study demonstrated enhanced anti-cancer immunity in PC-3 bearing nude mice and in a first generation PDX mode [8]. This model demonstrated increased tumour-associated NK cells after anti-sense treatments (PC-3), and in proliferation of patient tumour-associated CD8+ T-cells indicating that this transporter regulates the immune response.

In the following talk, Dr Rebecca Mather, a post-doctoral research associate at The Open University, then spoke about the long non-coding RNA landscape of NEPC [9,10]. This was approached from a screen of long non-coding RNAs in PDX models and clinical samples using databases prioritising dysregulated transcripts which were evolutionary conserved and up-regulated in NEPC. One of these transcripts *NEAR1* was functionally characterised using genetic techniques and was shown to regulate cell proliferation, survival and invasion. Mechanistically *NEAR1* was shown to act by driving transcription of the pioneer transcription factor, and proposed NEPC biomarker, FOXA2. Next generation anti-sense oligonucleotides are also being developed against this transcript as a possible therapy, and this transcript also shows promise as a urinary biomarker.

Finally, Dr Elena Jachetti, researcher at The Istituto Nazionale dei Tumori (Milan Italy) gave a lecture on stromal accomplices driving neuroendocrine features in prostate cancer. Using the TRAMP mouse models of prostate cancer Dr Jachetti focused on the mast cell component of the tumours, showing

that well-differentiated prostate adenocarcinomas need mast cells for *in vivo* tumour growth by provision of the matrix metalloprotease MMP9. Dr Jachetti then blocked mast cell degranulation (and therefore MMP9) in these models and found that despite the effect on adenocarcinoma growth, NEPC arose in these mice with greater incidence. Osteopontin was also discussed as another mediator released by mast cells. Indeed, Dr Jachetti showed that TRAMP mice knock-outs of osteopontin also had increased NEPC incidence. When Dr Jachetti then injected mast cells into these mice, the mast cells which were wild-type for osteopontin, but not osteopontin knock-out, reduced the frequency of NEPC tumours, indicating that osteopontin from mast cell was essential for this process [11,12].

Conclusion

In conclusion, the symposium has been a unique occasion to gather scientists and clinicians working on treatment-emergent NEPC, and to propose new molecularly-driven deadlines to accelerate research and improved the treatment of this deadly and poorly recognised malignancy. Key findings from this symposium are new guidelines for the prompt diagnosis and management of treatment-emergent NEPC, as well as molecular evidence indicating the importance of epigenetic factors, non-coding RNAs and tumour niche in the development of this deadly disease.

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